REMARKS

I. Status Summary

Claims 1-57 were pending in the subject U.S. patent application and subject to a Restriction/Election Requirement. Elected claims 1-5 and 7-11 are now pending and have been examined.

The specification has been objected to by the United States Patent and Trademark Office (hereinafter "the Patent Office") upon the contention that SEQ ID NO: 7 is seventeen (17) amino acids in length and thus cannot correspond to amino acids 2-17 of the GENBANK® Accession No. listed in Table 1.

Claims 1-5 and 7-11 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims.

Claims 1-5 and 7-11 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain phrases recited in the claims are unclear.

The specification has been amended to correct the numbering for the amino acids in GENBANK® Accession No. AAO26019 to which SEQ ID NO: 7 corresponds. Thus, no new matter has been added by the amendment to the specification.

Claims 5 and 11 have been canceled without prejudice.

Claims 1 and 7 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly in claims 5 and 11 as originally filed. As such, no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and in view of the remarks presented hereinbelow is respectfully requested.

II. Response to the Objections to the Specification

The specification has been objected to on the contention that SEQ ID NO: 7, which is seventeen (17) amino acids in length, cannot correspond to amino acids 2-17 of GENBANK® Accession No. AAO26019. Applicants have amended the relevant recitation in Table 1 of the specification to indicate that SEQ ID NO: 7 corresponds to amino acids 2-18 of GENBANK® Accession No. AAO26019. Support for this amended can be found in SEQ ID NO: 7 as filed in view of GENBANK® Accession No. AAO26019. Thus, no new matter has been added by the amendment to page 9 of the instant specification.

Applicants respectfully submit that the instant amendment addresses the objection to the specification, and respectfully request that it be withdrawn at this time.

III. Response to the Enablement Rejection

Claims 1-5 and 7-11 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims. According to the Patent Office, the only purpose for the method claimed is to repopulate the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian, and the specification does not provide a use for the method claimed without making a chimeric avian. The Patent Office also asserts that the absence of how to repopulate PGCs in an embryo in the art and the lack of correlative evidence in the specification fails to enable the method claimed, and further that the specification fails to overcome the absence in the art by reasonably teaching injecting donor PGCs into a treated embryo will repopulate the treated embryo to produce a viable chimeric avian. Additionally, the Patent Office asserts that it is not readily apparent from the specification that donor PGCs will target the proper position in the embryo to successfully replace the PGCs destroyed by the treatment so that a viable chimeric avian will be obtained, and if the method described does not produce viable chimeras, it would require those of skill undue experimentation to determine how to fix the problem because the specification provides no additional suggestions. The Patent Office thus contends that the claims are not enabled for its sole intended use; decreasing PGC numbers in an avian embryo for the purpose of repopulating the embryo with donor PGCs and obtaining a viable chimeric avian.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the Patent Office has adopted an improper framework for examining compliance of the instant application with the enablement provision of 35 U.S.C. § 112, first paragraph. Particularly, applicants respectfully submit that the Patent Office's attempt to merge the claimed methods with potential downstream uses for the avians created by practicing the claimed methods is believed to be improper.

For example, the Patent Office asserts that the only purpose for the method claimed is to repopulate the treated embryo with donor PGCs from a different strain or species of avian to make a chimeric avian, and the specification does not provide a use for the method claimed without making a chimeric avian (*see* Official Action at page 4). Applicants respectfully submit, however, that this is not the proper inquiry under the enablement provision of 35 U.S.C. § 112, first paragraph.

The proper framework for examination with respect to enablement is set forth in M.P.E.P. § 2164.01, which states in part:

> Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

M.P.E.P. § 2164.01 (emphasis added).

Applicants respectfully submit that the "claimed invention" in the instant application relates generally to methods of modulating PGC numbers in avian embryos. Applicants respectfully submit that the specification as filed is believed to enable one of ordinary skill in the art to decrease PGC numbers in an avian embryo (*see* claim 1 and dependents thereof) and inhibit development of PGCs in an avian embryo (*see* claim 7 and dependents thereof) by immunizing female birds with antigens associated with PGCs without undue experimentation. Applicants thus respectfully submit that the specification as filed is believed to fully comply with the requirements of 35 U.S.C. § 112, first paragraph, irrespective of whether or not the avians produced by the claimed methods themselves had a further downstream utility. Therefore, applicants respectfully submit that the instant rejection should be withdrawn at this time.

Furthermore, applicants respectfully submit that the Patent Office is incorrect in its assertion that the only purpose for the methods recited in the claims would be to repopulate a treated embryo with donor PGCs from a different avian strain or species to make a chimeric avian. Applicants respectfully submit that while this is a context for the claimed methods, it is not the only context that is disclosed in the specification.

To elaborate, applicants note that the Patent Office is correct that one of the embodiments of the presently claimed methods relates to repopulating a treated avian with PGCs from a different strain or species. For example, beginning on page 42, line 31, the specification as filed describes repopulation of the gonads of treated avians with PGCs from a different species.

Applicants further respectfully submit that the specification as filed also discloses the following:

> In particular embodiments of the presently disclosed subject matter, the number of endogenous PGCs in the recipient bird is reduced prior to introduction of the donor PGCs. In this manner, the donor PGCs can repopulate the gonads of the recipient bird and can increase the efficiency of producing chimeric birds and the proportion of gametes (and offspring) that are derived from the donor bird.

Specification at page 34 lines 19-26 (emphasis added). As such, applicants respectfully submit that after review of the instant specification, one of ordinary skill in the art would understand that one potential use of the instant methods would be to reduce endogenous PGCs in order to repopulate the embryo with PGCs from a donor (either of the same strain/species or a different strain/species) that had some genetic characteristic of value for which transfer to the recipient would be desirable (*i.e.*, to produce a chimeric bird having some desired genetic information). Applicants respectfully submit that one of ordinary skill in the art would understand that this donor could be a member of the same strain or species as the recipient, and thus the Patent Office's assertion that the only purpose for the methods recited in the claims would be to repopulate a treated embryo with donor PGCs from a different avian strain or species to make a chimeric avian is believed to be inaccurate.

However, applicants respectfully submit that this passage also discloses that practicing the instantly claimed methods to decrease PGC numbers and/or inhibit PGC development would also be useful for increasing the proportion of gametes present in the recipient avian that are derived from the donor. Applicants respectfully submit that one of ordinary skill in the art would understand that the role that PGCs play in vertebrate development is to colonize the gonads and thereafter differentiate into gametes. If the recipient's own PGC numbers are decreased and/or if endogenous PGC development is inhibited, then the transferred PGCs would be more likely to colonize the gonads, thereby increasing the proportion of gametes in the adult avian that are derived from the donor PGCs.

Additionally, applicants respectfully submit that the present specification also discloses that the claimed methods can be employed to alter the normal sex ratio of embryos by repopulation with, for example, "male" PGCs. Reference is made to page 42 of the instant specification beginning at line 16, which discloses the following:

> When used for increasing the number or ratio of male birds hatched from a group of eggs, the presently disclosed subject matter involves administering to a female bird in ovo male (*i.e.* ZZ) avian primordial germ cells. The gender of the bird in ovo can be predetermined or determined after hatch. The bird is then incubated to hatch, the gender of the bird determined if necessary, raised to sexual maturity, and bred by crossing the bird with a suitable male breeder stock in accordance with known techniques. A plurality of fertile eggs laid by that bird are then collected, and typically incubated to hatch and the resulting birds grown for at least two to three weeks. The ratio of male to female bird eggs (or birds) produced from the female bird is greater than that obtained in the absence of administering the male primordial germ cells to that bird in ovo. Such methods are typically used on species of bird that are raised for meat production, such as chickens, turkeys, ducks, etc.

Specification at page 42, lines 16-29.

Summarily, applicants respectfully submit that the Patent Office's assertion that the specification as filed only discloses interstrain or interspecific repopulation of embryos is believed to be inaccurate. As such, applicants respectfully submit that this assertion does not support the instant rejection of claims 1-5 and 7-11 under the enablement provision of 35 U.S.C. § 112, first paragraph.

And finally, even assuming *arguendo* that a purpose of the claimed methods is to prepare an avian for receiving donor PGCs, applicants traverse the Patent Office's assertions that (a) the absence of how to repopulate PGCs in an embryo in the art and the lack of correlative evidence in the specification fail to enable the method claimed; (b) the specification fails to overcome the absence in the art by reasonably teaching injecting donor PGCs into a treated embryo to repopulate the treated embryo to produce a viable chimeric avian; and (c) it is not readily apparent from the specification that donor PGCs will target the proper position in the embryo to successfully replace the PGCs destroyed by the treatment so that a viable chimeric avian will be obtained (*see* Official Action at pages 4-5). Particularly, applicants respectfully submit that the instant specification, various references that are currently of record in the instant prosecution, and certain additional references submitted herewith as part of an Information Disclosure Statement (IDS), demonstrate that PGCs can be isolated, cultured, and transferred to recipient avian embryos, where they migrate to and colonize the gonad of the recipient embryo to produce chimeric avians.

For example, applicants respectfully submit that Example 3 of the instant specification discloses isolating donor PGCs from chickens and transferring them to recipient chickens. Applicants further respectfully submit that contrary to the Patent Office's assertion, the techniques disclosed in Example 3 for isolation and transfer of avian PGCs would be well understood by one of ordinary skill in the art as of the instant filing date.

To elaborate, applicants direct the Patent Office's attention to page 31, line 29, through page 32, line 12 of the instant specification. This passage discusses the Vick *et al.*, 1993 and Bresler *et al.*, 1994 references (of record). Briefly, Vick *et al.*, 1993 discloses that PGCs can be obtained from normal sources in the developing avian (*see* Materials and Methods, beginning at page 179), transfected with defective retroviruses, and injected intravascularly into recipient embryos (*see* page 180, right column, first full paragraph), where they form chimeras (*see* Tables 2 and 3 and Figure 3 of Vick *et al.*, 1993). Similarly, Bresler *et al.*, 1994 discloses the isolation of PGCs from donor avians, the transfection of these cells with a *lacZ* expression

construct, and the intravascular transfer of these PGCs to recipients (*see* Materials and Methods, page 242). Bresler *et al.*, 1994 also discloses that recipient embryos showed a three-fold increase in PGC numbers in the gonads after transfer, indicating that the donor PGCs had properly migrated through the bloodstream to colonize the gonads (*see* Results on page 243).

Numerous additional references pertain to PGC isolation, manipulation, and transfer as of the filing date of the instant application, including, but not limited to Simkiss *et al.*, 1990 (isolation of PGCs from germinal crescent, transfection with a *lacZ* expression construct, and transfer back into the circulatory system where they migrate to and colonize the gonads); Naito *et al.*, 1994 (isolation and intravascular transfer of chicken PGCs, which gave rise to germline chimeras); Chang *et al.*, 1995 (isolation and culture of chicken PGCs, followed by intravascular transfer to recipients, where they migrated to and colonized the gonad to give rise to germline chimeras); Ono *et al.*, 1996 (intraspecific transfer of PGCs from quail to chick leading to gonadal chimerism); Ponce de Leon *et al.*, 1997 (long term PGC culture followed by transfer to recipients via the dorsal aorta led to production of germline chimeras); and Chang *et al.*, 1997 (isolation, culture, and transfer of donor PGCs into recipients resulted in germline chimera formation). Furthermore, applicants respectfully submit that U.S. Patent No. 6,691,638, which corresponds to U.S. Patent Application Publication No. 20030111016 referenced on page 32 of the instant specification, discloses that PGCs transferred to recipient avians can repopulate the gonads, and further that this can occur interspecifically (*see e.g.*, Example 15 and Table 1 of U.S. Patent No. 6,691,638).

Therefore, applicants respectfully submit that the assertions upon which the instant rejection is based, including but not limited to the Patent Office's assertions that the art lacked teaching as to how to repopulate PGCs in an embryo and that it is not readily apparent from the specification that donor PGCs will target the proper position in the embryo to successfully replace the PGCs destroyed by the treatment so that a viable chimeric avian will be obtained, are believed to be inaccurate. Therefore, applicants respectfully submit that these assertions do not support the instant rejection.

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of lack of enablement of claims 1-5 and 7-11. Claims 5 and 11 have been canceled, and thus the instant rejection is moot as to these claims. Thus, applicants respectfully request that the instant rejection of claims 1-4 and 7-10 be withdrawn and the claims allowed at this time.

IV. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-5 and 7-11 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain phrases appearing in the claims render the claims indefinite. Particularly, the Patent Office has asserted that the phrases "sufficiently high concentration of antibodies specific for the antigen to modulate the numbers [or development] of endogenous PGCs in an avian embryo" and "specific for the antigen" in claims 1 and 7 are unclear.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

IV.A. Response to the First Rejection

Claims 1-5 and 7-11 have been rejected by the Patent Office upon the contention that the phrase "sufficiently high concentration of antibodies specific for the antigen to modulate the numbers [or development] of endogenous PGCs in an avian embryo" renders the claims indefinite. According to the Patent Office, the concentration of antibodies required to decrease the number or development of PGCs is not set forth in the specification or the art at the time of filing, and thus those of skill would not be able to determine when the concentration of antibodies obtained was infringing on the claim.

Initially, applicants respectfully submit that M.P.E.P. § 2173.02 sets forth the proper framework for analyzing claim terminology. According to this section:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Additionally, an applicant "may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought" (M.P.E.P. § 2173.01).

Applicants respectfully submit that the instant rejection does not follow the framework set forth in M.P.E.P. § 2173.02 in that the Patent Office is not considering the instant phrase in the context of the claims as the phrase would be interpreted by one of ordinary skill in the art after consideration of the specification as a whole. Specifically, applicants respectfully submit that

the Patent Office appears to be requiring that the concentration of antibodies required to decrease the number or development of PGCs be explicitly disclosed as a unique value. However, applicants respectfully submit that this apparent requirement contradicts the M.P.E.P.'s specific endorsement regarding the use of functional language in claims, and thus is believed to be improper.

For example, applicants respectfully submit that claim 1 recites method for modulating primordial germ cells numbers in an avian embryo, the method comprising immunizing a female bird with an antigen associated with primordial germ cells, whereby an egg produced by the female bird comprises a sufficiently high concentration of antibodies specific for the antigen to decrease endogenous primordial germ cell (PGC) numbers in an avian embryo present within in the egg. Similarly, claim 7 recites a method for modulating primordial germ cell development in an avian embryo, the method comprising immunizing a female bird with an antigen associated with primordial germ cells, whereby an egg produced by the female bird comprises a sufficiently high concentration of antibodies specific for the antigen to inhibit development of primordial germ cells (PGCs) in an avian embryo present within the egg. Applicants respectfully submit that one of ordinary skill in the art would understand the claims to recite methods of decreasing PGC numbers or inhibiting PGC development by immunizing female birds with antigens such that immune responses directed against endogenous PGCs occur in embryonic birds. The consequence of the immune response is that the number of PGCs or the development of PGCs in the embryonic bird are decreases or inhibited, respectively.

With this in mind, applicants respectfully submit that one of ordinary skill in the art would understand after review of the instant specification how to assay PGC numbers in embryonic birds, and thus the outcome of the immunizing step (decreasing PGC numbers or inhibiting PGC development) would also be understood by one of ordinary skill in the art.

Accordingly, applicants respectfully submit that contrary to the Patent Office's apparent assertion, it is not necessary that an absolute antibody titer be disclosed in the specification as filed or in the art for one of ordinary skill in the art to understand the metes and bounds of the instant claims. Therefore, applicants respectfully submit that the instant rejection of claims 1-5 and 7-11 is believed to be improper. Claims 5 and 11 have been canceled, and thus the instant rejection is moot as to these claims. As such, applicants respectfully request that the instant rejection of claims 1-4 and 7-10 be withdrawn, and that the claims be allowed at this time.

IV.B. Response to the Second Rejection

Claims 1-5 and 7-11 have also been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the metes and bounds of what applicants consider antibodies "specific

for the antigen" are unclear. According to the Patent Office, it cannot be determined how specific the antibodies must be. The Patent Office thus contends that those of skill would not be able to determine whether antibodies that recognized any DAZL antigen, for example, were encompassed by the claim of if the phrase was limited to antibodies that are specific to a particular DAZL antigen such as DAZL-C or DAZL-N.

Applicants submit that similar to the case discussed hereinabove with response to the previous rejection, the Patent Office is basing the instant rejection upon a consideration of functional language without interpreting this language in the context of the claim and from the perspective of one of ordinary skill in the art.

To elaborate, applicants respectfully submit that the phrase at issue appears in claim 1 in the following context: method for modulating primordial germ cells numbers in an avian embryo, the method comprising immunizing a female bird with an antigen associated with primordial germ cells, whereby an egg produced by the female bird comprises a sufficiently high concentration of antibodies specific for the antigen to decrease endogenous primordial germ cell (PGC) numbers in an avian embryo present within in the egg. Applicants respectfully submit that this language relates to an outcome of the immunizing step: a decrease in PGC numbers in the developing embryo. Applicants respectfully submit that the decrease results from an immune response by the immunized female against the "antigen associated with primordial germ cells". This immune response leads to the deposition of anti-antigen antibodies in the egg, which thereafter bind to the antigen associated with primordial germ cells present on the endogenous PGCs during their development and/or migration, resulting in a decrease in the number of PGCs in the developing embryo (*see* specification at page 11, line 17 *et seq.*).

Applicants respectfully submit that after review of the specification, one of ordinary skill in the art would understand the metes and bounds of "specific for the antigen" to include antibodies that are capable of binding to the antigen to decrease PGC numbers in an avian embryo present within an egg as recited in claim 1.. Applicants respectfully submit that given this understanding, it is not necessary that a specific value for antibody specificity be disclosed in the specification.

Furthermore, applicants respectfully submit that the Patent Office's assertion that those of skill would not be able to determine whether antibodies that recognized any DAZL antigen, for example, were encompassed by the claim of if the phrase was limited to antibodies that are specific to a particular DAZL antigen such as DAZL-C or DAZL-N does not support the instant rejection. Applicants respectfully submit that claim 1 recites *inter alia* immunizing a female bird with an antigen associated with primordial germ cells, whereby an egg produced by the female

bird comprises a sufficiently high concentration of antibodies specific for the antigen to decrease endogenous PGC numbers in an avian embryo present within in the egg. Therefore, applicants respectfully submit that one of ordinary skill in the art would understand that the claim relates to generating an immune response in the immunized female that results in antibodies sufficiently specific for the antigen associated with PGCs being deposited in the egg.

Thus, the "particular DAZL antigen" would in some embodiments be the antigen associated with PGCs with which the female was immunized. Given that this antigen would be identifiable by one of ordinary skill in the art when the immunizing step was performed, applicants respectfully submit that the Patent Office has identified no situations under which the relevant antigen, such as a DAZL antigen, would not be known.

Applicants respectfully submit that an identical approach can be followed for the phrase at issue in the context of claim 7. In this case, the claim recites *inter alia* that the development of PGCs is inhibited by the presence of the antibody. Here as well, the antigen associated with PGCs is the antigen against which the female's immune response is generated, and thus the antigen would be known during performance of the immunizing step.

And finally, it appears that the Patent Office is again requiring that a specific antibody titer would have to be disclosed in order to provide how specific the antibodies need to be. However, applicants respectfully submit that after consideration of the instant specification, one of ordinary skill in the art would understand that the antibodies need to be specific enough to decrease PGC numbers or inhibit PGC development. Thus, the use of the functional language to describe the outcome of performing the claimed methods is believed to be acceptable under M.P.E.P. §§ 2173.01 and 2173.02.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of lack of compliance of claims 1-5 and 7-11 with the second paragraph of 35 U.S.C. § 112. Therefore, applicants respectfully request that the instant rejection of claims 1-5 and 7-11 be withdrawn at this time. Applicants further respectfully submit that claims 1-5 and 7-11 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: January 7, 2008 By: 

Arles A. Taylor, Jr.
Registration No. 39,395
Customer No. 25297
(919) 493-8000

297/204 PCT/US AAT/CPP/dbp